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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/827,133	ALLEN ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23,25,26,28 and 29* is/are rejected.

7)☒ Claim(s) *24 and 27* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-29 are pending in the instant application.

Claim Objections

Claims 24 and 27 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims 24 and 27 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-23, 25 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 recites the limitation "said addition" in line 4 of the claim. There is insufficient antecedent basis for this limitation in the claim. For the purposes of examination, the phrase starting with the recitation of "said addition" has been interpreted as further limiting the modification of the protein as set forth in lines 1-3 of the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 7, 15, 17, 19-23, 25, 26, 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Leclerc et al (Biotechniques, Vol. 29, No. 3, pages 590-601, 2000; see the entire reference).

Leclerc et al teach a gene cassette comprising a firefly luciferase coding sequence modified by the addition of the mODC PEST sequence, which reduces the duration of bioluminescence relative to the unmodified sequence (e.g. Figures 1 and 2; pages 591-592, Molecular Cloning, PCR Amplification and DNA Sequencing). Leclerc et al teach the determination of the duration of luminescence by comparing a time course of luminescence emitted by the modified and unmodified proteins (e.g. pages 594-595, Luciferase Assay Conditions; Figure 2). Leclerc teach a half-life of 0.84 h for the modified luciferase and a half-life of 3.68 h for the unmodified luciferase. Thus, absent any evidence to the contrary, one would necessarily expect that decrease in the duration of activity of the modified luciferase is 100-fold to 1000-fold lower than the unmodified protein. Further, Leclerc et al teach a plasmid comprising the gene cassette (e.g. pages 591-592, Molecular Cloning, PCR Amplification and DNA Sequencing). The plasmid is capable of expressing the modified luciferase protein in mammalian cells (e.g. Figure 2). Leclerc et al teach *E. coli* and mammalian cells comprising the

plasmid (e.g. page 591, Molecular Cloning, PCR Amplification and DNA Sequencing; page 591, T-47D Cell Culture, chemical Transfection and Microinjection; Figures 2 and 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14, 19-24 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Andersen et al (Applied and Environmental Microbiology, Vol. 64, No. 6, pages 2240-2246, 1998; see the entire reference) in view of Hakkila et al (Analytical Biochemistry, Vol. 301, pages 235-242, February 2002; see the entire reference).

Andersen et al teach plasmid vectors comprising gene cassettes comprising modified green fluorescent proteins (GFP) (e.g. Table 1; page 2241, Plasmids). The modifications of the

GFP coding sequence taught by Andersen et al include the addition of a nucleic acid encoding a peptide that specifically binds to a tail-specific protease (e.g. page 2240, paragraph bridging columns; page 2243, Construction of unstable Gfp variants). Andersen et al teach the modification of the GFP coding sequence with the addition of a nucleic acid encoding the following peptide sequences: AANDENYAAAV, AANDENYALAA, AND AANDENYAASV, which are the sequences contained in SEQ ID NOS: 8, 9 and 10, respectively, of the instant application. Further, Andersen et al teach that the plasmid vector comprising the modified GFP gene cassette is a vector suitable for driving expression in a bacterial cell (e.g. page 2241, Plasmids; Table 1). Moreover, Andersen et al teach the comparison of the duration of fluorescence by comparing a time course of a first measure of fluorescence emitted by the modified GFP and a time course of a second measure of fluorescence emitted by the unmodified GFP (e.g. paragraph bridging pages 2241-2242; page 2242, right column; page 2244, 1st full paragraph). Andersen et al conclude that the *in vivo* half-life of the unmodified GFP is more than one day, whereas the half-life of the modified GFPs are approximately 60 min and 110 min (e.g. page 2244, right column, 1st full paragraph). Further Andersen et al state, "the half-life estimates obtained in the experiments presented are not to be taken as absolute, fixed values. The protease reaction resulting in degradation of Gfp may be dependent on strains, growth conditions, specific features of the surroundings, competing targets in the cell, etc." (see the paragraph bridging pages 2244-2245). Thus, absent any evidence to the contrary, one would necessarily expect that the addition of a tail-specific proteases tag sequence to a protein is capable of causing a decrease in the duration of activity of 100-fold to 1000-fold lower than an unmodified protein.

Andersen et al do not teach the modification of a bioluminescent protein such as LuxA and/or LuxB of the LuxCDABE operon. Anderson et al do not explicitly teach bacteria comprising the plasmid comprising the coding sequence for the modified protein.

Hakkila et al teach that the nucleic acids comprising the luxCDABE operon from *Vibrio fischeri*, *Vibrio harveyi*, and *Photorhabdus luminescens* are known in the art (e.g. page 235, right column). The luxCDABE operon comprises both LuxA and LuxB (e.g. page 235, right column). Hakkila et al teach the plasmid pmerRluxCDABE and *E. coli* bacteria comprising the plasmid (e.g. Table 1; page 236, right column, 1st full paragraph; bottom of page 237; page 238, *Cultivation of the Bacteria*; Figure 1). Further, Hakkila et al teach that luciferases, such as the LuxAB luciferase of the LuxCDABE operon, give detectable signals faster and at lower analyte concentrations in whole bacterial sensors as compared to fluorescent proteins such as GFP (e.g. page 239, paragraph bridging columns). Hakkila et al state, "The results indicate that luciferases are better reporters in whole-cell sensor bacteria" (see the Abstract). Moreover, Hakkila et al teach that the rapid detection of luciferase can be accomplished with instrumentation that is less complex than the equipment required for the detection of GFP (e.g. page 241, left column, 2nd full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Andersen et al to replace the GFP coding sequence with that of LuxA and LuxB in the form of the LuxCDABE operon of Hakkila et al because Andersen et al teach it is within the ordinary skill in the art to use a tail-specific protease coding sequence to modify the coding sequence of a reporter gene and Hakkila et al teach the use of recombinant

DNA technology for the cloning and expression of the LuxCDABE operon and GFP proteins for use as reporter genes.

One would have been motivated to make such a modification in order to receive the expected benefit of quicker and more sensitive detection of analytes in whole-cell sensor bacteria as taught by Hakkila et al. Further, one would have been motivated to modify the LuxA and/or LuxB sequences of Hakkila et al with the tail-specific protease tag coding sequences of Andersen et al to observe fast dynamic phenomena. The modified luciferase would be better adapted to quickly identify an analyte due to the benefits of the luciferase protein, as taught by Hakkila et al, and quicker to turn-off a signal in the absence of analyte due to the benefits of the tail-specific protease tag, as taught by Andersen et al. Moreover, one would be motivated to replace the GFP coding sequence with that of a luciferase coding sequence to decrease the complexity of the instrumentation required to detect the reporter gene expression. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1, 2, 7, 15-21, 25, 26, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vieites et al (Yeast, Vol. 10, No. 10, pages 1321-1327, 1994; see the entire reference) in view of Mateus et al (Yeast, Vol. 16, pages 1313-1323, 2000; see the entire reference) as evidenced by Berset et al (Molecular and Cellular Biology, Vol. 22, No. 13, pages 4463-4476, 2002; see the entire reference).

Vieites et al teach a plasmid vector comprising a gene cassette encoding *Photinus pyralis* luciferase gene operably linked to an ADH1 or GAL promoter for expression in yeast such as *Saccharomyces cerevisiae* (e.g. page 1322, *Plasmids*; Figure 1). Vieites et al teach that the luciferase gene cassette can be used as a highly reliable, sensitive, null-background and non-toxic method for measuring gene expression *in vivo* in yeast (e.g. page 1321, paragraph bridging columns). Vieites et al teach yeast comprising the plasmid vector (e.g. page 1322, *Optimization of technical parameters*). Vieites et al teach the measurement of bioluminescence over time (e.g. page 1322, *Luciferase assay*; paragraph bridging pages 1322-1323; Figure 2). Further, Vieites et al teach that the gene cassette may be used for the study of weak promoters, which, prior to the development of this assay, could only be studied by other less sensitive methods (e.g. paragraph bridging pages 1326-1327).

Vieites et al do not teach a modification of the luciferase sequence, wherein the modification is an addition of a peptide sequence that specifically binds to SCF(Grr1) or is a PEST-rich sequence of the c-terminus of G1 cyclin (*Cln2*). Vieites et al do not teach the measurement of the duration of bioluminescence as a time course for the modified luciferase sequence.

Mateus et al teach a plasmid comprising a nucleic acid sequence encoding a fusion of green fluorescent protein, wherein the nucleic acid sequence has been modified by the addition of the 3'-terminal 534 nucleotides of CLN2 (e.g. pages 1314-1315, Strains and Plasmids). Mateus et al teach that the 3'-terminal fragment of CLN2 comprises a PEST motif (e.g. page 1314, paragraph bridging columns. Further, Mateus et al teach that the 178 residues encoded by the 534 nucleotides of CLN2 to either GFP or a thymidine kinase derivative results in a decrease

in half-life of the tagged protein (e.g. page 1320, paragraph bridging columns; paragraph bridging pages 1315-1316). After measuring the duration of fluorescence of the modified and unmodified GFP, Mateus et al teach that the half-life of the modified GFP is about 34 min and the unmodified GFP is about 7 h 23 min in *S. cerevisiae* cells (e.g. Figure 1; paragraph bridging pages 1316-1317). Thus, absent any evidence to the contrary, one would necessarily expect that the addition of a CLN2 3-terminal tag sequence to a protein is capable of causing a decrease in the duration of activity of 100-fold to 1000-fold lower than an unmodified protein. Moreover, Mateus et al teach that the destabilization of a reporter of gene expression allows the reporter to be used as a measure of gene switch-off, whereas the stable version of the reporter is not suitable if the half-life is long enough to obscure the switch-off (e.g. paragraph bridging pages 1313-1314).

Berset et al teach that the 178 terminal amino acid residues of G1 cyclin (Cln2p) comprise a PEST domain and a D domain (e.g. Figure 3A). Further, Berset et al teach that the D domain interacts with SCF(Grr1) (e.g. paragraph bridging pages 4469-4470). Thus, the nucleic acid sequence taught by Mateus et al encodes both a PEST-rich sequence and an SCF(Grr1) binding sequence.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the gene cassette and plasmid vector of Vieites et al to include the destabilizing fragment taught by Mateus et al because both Vieites et al and Mateus et al teach it is within the ordinary skill in the art to use reporter genes to monitor gene expression in *Saccharomyces cerevisiae*. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the gene cassette and plasmid vector of Vieites et

al to include the destabilizing fragment taught by Mateus et al because Mateus et al teach that the 3'-terminal fragment is a destabilization domain that is transferable to different coding sequences. Moreover, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the time course measurement of luciferase activity of Vieites et al to include the measurement of the modified luciferase.

One would have been motivated to make such a modification in order to receive the expected benefit of being able to measure the switch-off of gene transcription using a reporter gene as taught by Mateus et al. Further, one would have been motivated to destabilize the luciferase gene of Vieites et al to measure the switch-off of gene transcription because luciferase is a highly reliable, sensitive, null-background and non-toxic reporter. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Citation of Relevant Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Knudsen et al. tmRDB (tmRNA database). Nucleic Acids Res. Vol. 29, No. 1, pp. 171-2, January 2001.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached at 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jennifer Dunston
Examiner
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jad

TERRY MCKELVEY
PRIMARY EXAMINER